acid to a corresponding amino acid in the framework region of the heavy chain of the human III2R antibody; and

b) a second nucleic acid sequence encoding at least a portion of a constant region of an immunoglobulin of human origin.

REMARKS

I. The Specification

The Examiner has objected to the drawings, which allegedly fail to comply with 37 CFR § 1.184. Corrected drawings in compliance with these requirements are submitted herewith.

The specification is amended herein to merely correct a typographical error; the term "I2R" has been replaced with "III2R". Support for this correction can be found at least at page 35 of the specification which indicates that human heavy chain framework sequences that were used to humanize the 3D1 antibody were from the human subgroup I (see e.g., page 35, lines 13-17). Page 35 of the specification also states that the heavy chain framework sequences were published by Manheimer-Lory, A. *et al.*, J. Exp. Med. 174(6):1639-1652 (1991) (a copy is enclosed with the concurrently filed Information Disclosure Statement). Table I of the Manheimer-Lory reference teaches only two cell lines with the heavy chain variable regions belonging to subtype I: the III2R cell line and the R3.5H5G cell line. It is clear that the use of the term "I2R" rather than "III2R" throughout the specification and claims was a typographical error. Accordingly,

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

the term "I2R" has been replaced with "III2R" at each occurrence in the specification and in claims 1, 25, 33, and 75. No new matter has been added.

II. Status of the Claims

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46, and 64-76 belong to the elected group and are pending in this application. Claims 1, 2, 8, 15, 21, 25, 30, 33, 40, and 75 have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. Support for these amendments and new claims can be found throughout the specification and claims as originally filed, as discussed below. No new matter has been added.

III. Enablement Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46, and 64-76 were rejected under 35 U.S.C. § 112, First Paragraph as the Examiner asserts that the "3D1", "H2F", "I2R" [III2R] antibodies and the CRL-12524 cell line are not readily available to the public. Office Action dated June 25, 2001, at page 2.

A. The 3D1 Antibody

Applicants hereby submit the entire nucleotide and amino acid sequence for the 3D1 antibody in paper form, thereby making the antibody available to the public. A sequence listing containing the nucleotide and amino acids will be submitted separately on Friday, August 30, 2002. Accordingly, Applicants request that the rejection be withdrawn.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

B. The I2R (III2R) and H2F Antibodies

Applicants have previously argued that only the amino acid sequence from the framework region of the III2R and H2F antibodies is required to be disclosed to one of ordinary skill in the art to make and use the invention. These sequences are available in Manheimer-Lory, J. Exp. Med., 174:1639-1652 (1991). Amendment dated April 17, 2001, at page 9.

The Examiner has rejected this argument, saying that the entire amino acid sequences of the antibodies must be provided or that hybridomas expressing the antibodies need to be deposited. Office Action dated June 25, 2001, at pages 2-3.

Applicants believe that there has been a misunderstanding regarding the invention. In this invention, a chimeric antibody was made by combining the constant region of a human immunoglobulins (such as IgG2 or IgG4) with a variable region of a non-human antibody (such as the mouse 3D1 antibody) This chimeric antibody was then humanized. This process entailed comparing the sequence of the variable regions of the chimeric antibody to the published sequence of the variable regions of two human antibodies (III2R and H2F).[1] During this comparison of the printed sequences of the variable regions of the antibodies, the inventors examined the framework sequences of the chimeric antibody and then modified on the cDNA level to more closely resemble the natural sequences in the framework region of a human antibody based on the

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

[1] The published sequences of the III2R and H2F antibodies were obtained from Manheimer-Lory, A. *et al.*, *J. Exp. Med.* 174(6):1639-52 (1991).

sequences of the III2R and/or H2F antibodies (i.e. certain non-human framework amino acids were substituted with corresponding human framework amino acids).

The Examiner appears to believe that the III2R and H2F antibodies were used as reagents in the preparation of the claimed invention. This is not the case.

Namely, portions of the III2R and H2F antibodies were not physically spliced and inserted into the chimeric antibody. Rather, Applicants relied on the printed and disclosed sequences of the variable regions in Manheimer-Lory and compared them on paper to the variable region sequences of the chimeric antibody to determine appropriate alterations to be made to the non-human portion of the chimeric antibody. Thus, the III2R and H2F antibodies themselves were never physically used as reagents to arrive at the claimed invention. Because the antibodies themselves were not used as reagents, Applicants argue that it is not necessary for the entire amino acids of these antibodies or hybridomas that produce these antibodies to be disclosed.

This concept is illustrated at page 36, lines 14-17, which states that "based on a sequence homology, I2R [III2R] was selected to provide the framework for the humanized 3D1 heavy chain and H2F was selected for the humanized 3D1 light chain variable region." (Citing Manheimer-Lory). The specification at page 39, lines 13-14 says that "the CDRs in the humanized 3D1 heavy and light chains can accommodate substitutions of amino acids from the corresponding positions of I2R [III2R] frameworks."

Claims 1, 21, 25, 30, 33, 40, and 75 have been amended to clarify this aspect of the invention, reciting that the immunoglobulin comprises at least one framework region

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of the H2Fand/or III2R antibodies.

Accordingly, because the framework regions of the H2F and III2R antibodies were used in a paper comparison of the antibodies, were only used as a sequence template, and the antibodies themselves were not used as reagents to arrive at the claimed invention, Applicants submit that the rejection should be withdrawn.

C. The CRL-12524 cell line

Page 13, lines 12-14 of the specification states that this cell line was deposited in the A.T.C.C. on May 5, 1998, and afforded Accession Number CRL-12524. Applicants provide a copy of the Deposit Disclosure. Furthermore, Applicants enclose a Microorganism Deposit Declaration stating that in accordance with the Budapest Treaty, Genetics Institute will irrevocably remove any restrictions as to the public availability of this culture deposit upon grant of the patent. Accordingly, Applicants request that the rejection be withdrawn.

IV. Definiteness Rejection Under 35 U.S.C. § 112, Second Paragraph

A. Antibody Rejections

Claims 1-12, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46, and 64-76 were rejected under 35 U.S.C. § 112, Second Paragraph because the characteristics of the "3D1", "H2F", and "I2R" [III2R] antibodies were allegedly unknown. Office Action at page 4.

By providing the entire sequence of the 3D1 antibody, Applicants submit that the characteristics of this antibody are now publicly known.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Based on the arguments stated above, Applicants submit that it is not necessary for the public to know the complete characteristics of the H2F and III2R antibodies because the framework regions were used which are disclosed in Manheimer-Lory. In support of the argument that the entire antibody need not be characterized, the invention was made without Applicants' knowledge of the full characteristics of the antibodies. Instead, Applicants only used the sequences of the framework region disclosed in this reference, and compared the paper version of the sequence with the framework region of the sequence of the chimeric antibody to ascertain which amino acids in the chimeric antibody should be substituted. Applicants have amended claims 1, 21, 25, 30, 33, 40, and 75 to clarify this point, reciting that the immunoglobulin comprises at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of the H2Fand/or III2R antibodies.

B. Rejection for the Definition of "Stringent Conditions"

Claims 24 and 28 were rejected as being indefinite because the Examiner contends that the metes and bounds of the term "stringent conditions" are ambiguous and unclear, and in turn, the metes and bounds of the claimed nucleic acids are not defined. Office Action dated June 25, 2001, at page 5.

Applicants contend that the definition of "stringent conditions" is well known to one of ordinary skill in the art. In support of this contention, Applicants provide the following citations that provide definitions of "stringent conditions". Copies of the pertinent pages are enclosed for your convenience.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

"Stringent hybridization conditions" are described in Ausubel, F.M., *et al.*, Eds. *Current Protocols in Molecular Biology*, Greene Publishing Associates and John Wiley and Sons Inc. (1993). Book I, section 6.3.4-6.3.6 provides two high stringency wash buffers. The first buffer contains 0.2X SSC and 0.1% SDS. The second buffer contains 1mM Na_2EDTA, 40 mM $NaHPO_4$, pH 7.2, and 1% SDS. High stringency hybridization conditions are performed at temperatures as high as 65° to 70°C. This reference is cited in the second full paragraph of page 27 of the specification and is incorporated by reference at page 54 of the specification. Therefore, one of ordinary skill in the art would have known what Applicants regarded as the invention with respect to this term.

An additional protocol for performing high stringency hybridization is disclosed in Sambrook, *et al.*, *Molecular Cloning,* 2nd Edition, Cold Spring Harbor Laboratory Press (1989). Book 1, section 1.103 states high stringency experiments can be performed by washing for 60 minutes in a solution of 0.2X SSC and 0.1% SDS at 68°C. This reference is widely used by those of ordinary skill in the art and thus, this the definition of the term "stringent conditions" would be readily available to one of ordinary skill in the art.

Accordingly, Applicants submit that the term "stringent conditions" is definite and respectfully request reconsideration and withdrawal of the rejection of claims 24 and 48 under 35 U.S.C. § 112, second paragraph.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

V. Obviousness Rejection under 35 U.S.C. § 103(a)

Claims 1-2, 15, 21, 23-25, 27, 28, 30-36, 38-40, 46, and 64-76 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Freeman *et al.* (U.S. Patent No.

6,084,067) in view of gene cloning and expression strategies for deriving recombinant antibodies and fragments thereof. The Examiner contends that it would have been a matter of routine experimentation to arrive at the instant invention. He notes that Freeman discloses the HF2.3D1 antibody and teaches that it may be humanized. He relies on alleged common knowledge in the art to modify Freeman to arrive at the instant invention.

To establish a *prima facie* case of obviousness in this case, basic criteria must be met. First, the reference, knowledge commonly known in the art, or the combination of the two must teach or suggest each and every element of the instant invention. Second, there must be a reasonable expectation of success. M.P.E.P. § 2143.

Regarding the first element, independent claims 1, 15, 21, 25, 30, 33, 40, and 75 have been amended to recite the limitation the humanized immunoglobulins of the claimed invention having a "binding affinity of at least about 10^7 M^{-1}. This binding affinity is comparable to that of the native antibody (see Figure 3). This amendment is supported in the specification at page 10, line 19. This limitation is not found in Freeman and is not commonly known to one of ordinary skill in the art. Specifically, the art recognized that prior humanized antibodies generally lost much of their binding specificity, as discussed below. The art contained no teachings or suggestions that humanized antibodies that retained their binding affinity could be prepared.

Because the claimed invention discloses this feature, which is not taught or suggested in the art, Applicants assert that the claimed invention is not obvious.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Regarding the requirement that there be a reasonable expectation of success, Applicants contend that the success of their invention is unexpected. Applicants note that is not always simple to prepare a humanized antibody with antigen binding properties comparable to those of the starting murine antibody. This is illustrated in the following references, submitted in the concurrently filed Information Disclosure Statement. For example, Queen *et al.* teaches that the modified antibodies taught therein have approximately one third the binding activity of the starting murine antibodies (P.N.A.S. 86:10029 (1989), Abstract). Co *et al.* (P.N.A.S. 88:2869, 2869 (1991) teach that:

> generation of other fully humanized antibodies has proved unexpectedly difficult because significant loss of binding affinity generally resulted from simple grafting or hypervariable regions, probably due to distortion of the complementarity-determining region (CDR) conformation by the human framework.

Other references also teach that modification of human framework regions can lead to a significant loss of binding affinity to the antigen (*See, e.g.*, Tempest *et al.*, Biotechnology, 9:266 (1992) and Shalaby *et al.*, J. Exp. Med. 17:217 (1992)).

The specification shows that humanized antibodies are based on the murine 3D1 antibody which has a comparable binding affinity to the murine antibody. More specifically, results showed that both humanized IgG4 and humanized IgG2.M3 anti-B7-2 antibodies have a similar high binding affinity as the murine 3D1 antibody, indicating no loss of affinity for B7-2 with these particular humanizations of the 3D1 antibody (see Figure 3). Maintaining such high affinity, without loss due to the humanization process was very surprising. Thus, despite the difficulty of such an undertaking, Applicants

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

provide and claim an inventive, enabled invention which comprises successfully humanizing individual antibodies without loss of binding affinity.

For all of these reasons, Applicants submit that the rejection under 35 U.S.C. § 103(a) is improper, and ask that it be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this filing and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: August 28, 2002

By: _____
Rebecca M. McNeill
Reg. No. 43,796

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

APPENDIX OF AMENDMENTS

IN THE SPECIFICATION:

Paragraph at page 2, beginning at line 20:

The invention also embodies a humanized immunoglobulin having a binding specificity for B7-2 comprising a heavy chain and/or a light chain. The light chain comprises a CDR (e.g., CDRI, CDR2 and CDR3) derived from an antibody of nonhuman origin which binds B7-2 and a FR derived from a light chain of human origin (e.g., H2F antibody). The heavy chain comprises a CDR (e.g.,CDRI, CDR2 and CDR3) derived from an antibody of nonhuman origin which binds B7-2 and a FR region derived from a heavy chain of human origin (e.g., the human [I2R] III2R antibody). The immunoglobulin can further comprise CDR1, CDR2 and CDR3 for the light or heavy chain having the amino acid sequence set forth herein or an amino acid.

Paragraph at page 3, beginning at line 18:

Another embodiment of the invention is a humanized immunoglobulin heavy chain that is specific for B7-2 and comprises CDRI, CDR2 and/or CDR3 of the heavy chain of the 3D1 antibody, and a human heavy chain FR (e.g., [I2R] III2R antibody). The invention pertains to a humanized immunoglobulin heavy chain that comprises a variable region shown in Figure 2A (SEQ ID NO: 6). The invention also pertains to an isolated nucleic acid sequence that encodes a humanized variable heavy chain specific for B7-2 that comprises a nucleic acid, such as the sequence shown in Figure 2A (SEQ

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

ID NO: 5), a nucleic acid that encodes the amino acid sequence shown in Figure 2A (SEQ ID NO: 6), a nucleic acid which hybridizes thereto under stringent hybridization conditions, and a nucleic acid which is the complement thereof.

Paragraph at page 36, beginning at line 4:

To retain the binding affinity of the mouse antibody in the humanized antibody, the general procedures of Queen *et al.* were followed (Queen *et al. Proc. Natl. Acad Sci. USA* 86: 10029 (1989), U.S. Patent Nos. 5,585,089 and 5,693,762, the teachings of which are incorporated herein in their entirety). The choice of framework residues can be critical in retaining high binding affinity. In principle, a framework sequence from any human antibody can serve as the template for CDR grafting; however, it has been demonstrated that straight CDR replacement into such a framework can lead to significant loss of binding affinity to the antigen (Tempest *et al.*, *Biotechnology* 9: 266 (1992); Shalaby *et al.*, *J. Exp. Med.* 17: 217 (1992)). The more homologous a human antibody is to the original murine antibody, the less likely the human framework will introduce distortions into the mouse CDRs that could reduce affinity. Based on a sequence homology, [I2R] III2R was selected to provide the framework for the humanized 3D1 heavy chain and H2F for the humanized 3D1 light chain variable region. Manheimer-Lory, A. *et al.*, *J. Exp. Med.* 174(6):1639-52 (1991). Other highly homologous human antibody chains would also be suitable to provide the humanized antibody framework, especially kappa light chains from human subgroup 4 and heavy chains from human subgroup 1 as defined by Kabat.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Paragraph at page paragraph at page 36, beginning at line 21 (and continuing to page 37, line 3) with:

Normally the heavy chain and light chain from the same human antibody are chosen to provide the framework sequences, so as to reduce the possibility of incompatibility in the assembling of the two chains. The [I2R] III2R antibody shows a high homology to the 3D1 heavy and light chains and thus, was chosen to provide the framework for the initial humanized antibody model. The 3D1 light chain variable region, however, shows a significantly higher homology to the H2F framework compared to any others, including [I2R] III2R. Therefore, H2F was chosen instead to provide the framework for the humanized 3D1 light chain variable region, while [I2R] III2R was selected to provide the framework for the heavy chain variable region.

Paragraph at page 37, beginning at line 4:

The computer programs ABMOD and ENCODE (Levitt *et al.*, *J. Mol. Biol.* 168: 595 (1983)) were used to construct a molecular model of the 3D1 variable domain, which was used to locate the amino acids in the 3D1 framework that are close enough to the CDRs to potentially interact with them. To design the humanized 3D1 heavy and light chain variable regions, the CDRs from the mouse 3D1 heavy chain were grafted into the framework regions of the human [I2R] III2R heavy chain and the CDRs from the mouse 3D1 light chain grafted into the framework regions of the human H2F light chain. At framework positions where the computer model suggested significant contact with

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

the CDRs, the amino acids from the mouse antibody were substituted for the original human framework amino acids. For humanized 3D1, this was done at residues 27, 30, 48, 67, 68, 70 and 72 of the heavy chain and at residue 22 of the light chain. Furthermore, framework residues that occurred only rarely at their positions in the database of human antibodies were replaced by a human consensus amino acid at those positions. For humanized 3D1 this was done at residue 113 of the heavy chain and at residue 3 of the light chain.

Paragraph at page 39, beginning at line 12:

Likewise, many of the framework residues not in contact with the CDRs in the humanized 3D1 heavy and light chains can accommodate substitutions of amino acids from the corresponding positions of [I2R] III2R and H2F frameworks, from other human antibodies, from the mouse 3D1 antibody, or from other mouse antibodies, without significant loss of the affinity or non-immunogenicity of the humanized antibody. Table 2 lists a number of additional positions in the framework where alternative amino acids may be suitable.

IN THE CLAIMS:

1. (Twice Amended). A humanized immunoglobulin having binding specificity for B7-2, wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, and wherein said immunoglobulin comprises [comprising] an antigen binding region of non-human origin and at least a portion of an immunoglobulin of human origin, further

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

wherein the antigen binding region of non-human origin comprises [a heavy chain derived from I2R antibody or a light chain derived from the H2F antibody] at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the III2R heavy chain framework region or the H2F light chain framework region.

2. (Twice Amended). The humanized immunoglobulin of Claim 1, wherein the portion of an immunoglobulin of human origin is [derived from] a human constant region.

8. (Amended). The humanized immunoglobulin of Claim 1, wherein the antigen binding region comprises a complementarity determining region of rodent origin, and the portion of an immunoglobulin of human origin is [derived from a] at least a portion of a human framework region.

15. (Twice Amended). A humanized immunoglobulin having binding specificity for B7-2, wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, and wherein said [which] humanized immunoglobulin is derived from the cell line deposited with the ATCC®, Accession No. CRL-12524.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

21. (Twice Amended). A humanized immunoglobulin light chain having binding specificity for B7-2 , wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, and wherein said immunoglobulin comprises [comprising] CDR1, CDR2 and

CDR3 of the light chain of the murine 3D1 antibody, and [a human light chain framework region origin derived from] further wherein the immunoglobulin comprises at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of the light chain of the human H2F antibody.

25. (Twice Amended). A humanized immunoglobulin heavy chain specific for B7-2 wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, and wherein said immunoglobulin comprises [comprising] CDR1, CDR2 and CDR3 of the heavy chain of the muring 3D1 antibody, and [a human heavy chain framework region derived from] further wherein the immunoglobulin comprises at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of the heavy chain of the human III2R [IR2] antibody.

30. (Twice Amended). An expression vector comprising a fused gene encoding a humanized immunoglobulin light chain, said gene comprising a nucleotide sequence encoding a CDR derived from a nonhuman antibody having binding specificity for B7-2, wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, [and a framework region] further wherein the immunoglobulin comprises at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of [derived from] the light chain of the human H2F antibody.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

33. (Twice Amended). An expression vector comprising a fused gene encoding a humanized immunoglobulin heavy chain, said gene comprising a nucleotide sequence encoding a CDR derived from a heavy chain of a nonhuman antibody having binding specificity for B7-2, wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, [and a framework region] further wherein the immunoglobulin comprises at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of [derived from] the heavy chain of the human III2R [I2R] antibody.

40. (Twice Amended). A fused gene encoding a humanized immunoglobulin light chain having binding specificity for B7-2, wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, comprising:

a) a first nucleic acid molecule encoding an antigen binding region derived from the murine 3D1 monoclonal antibody, [comprising a framework region] further wherein the immunoglobulin comprises at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of [derived from] the light chain of the human H2F antibody; and

b) a second nucleic acid sequence encoding at least a portion of a constant region of an immunoglobulin of human origin.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

75. (Amended). A fused gene encoding a humanized immunoglobulin heavy chain having binding specificity for B7-2, wherein said immunoglobulin has a binding affinity of at least about 10^7 M^{-1}, comprising:

a) a first nucleic acid molecule encoding an antigen binding region derived from the murine 3D1 monoclonal antibody, [comprising a framework region] further wherein the immunoglobulin comprises at least one framework region containing a substitution of at least one amino acid to a corresponding amino acid in the framework region of [derived from] the heavy chain of the human III2R [I2R] antibody; and

b) a second nucleic acid sequence encoding at least a portion of a constant region of an immunoglobulin of human origin.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com